Multi-scale imaging to drive multi-scale models of treatment response

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Overview

Goal: extend a previously established 3D, tissue scale model, initialized and constrained by patient-specific quantitative imaging data, for predicting breast tumor response to therapy[1].

- Leverage *in vitro* tumor cell response data and corresponding modeling results for individual drugs to improve the predictive ability of the clinical model and explore alternate therapeutic strategies.
- Connect tissue and cellular scales by coupling drug effects into the growth and reduction terms of the governing equation for change in tumor cell number.

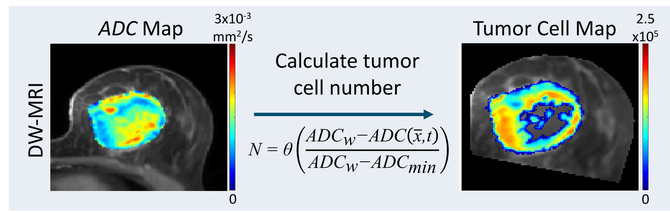
We posit that an integrated multi-scale mathematical-experimental approach bridging clinical and preclinical data can elucidate the optimal strategies for combination therapy for breast cancer.

Clinical Imaging Data and the Tissue Scale Model

Clinical Data

- Tumor ROIs are defined by enhancement in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) data.
- Diffusion-weighted (DW-) MRI data is used to estimate the apparent diffusion coefficient (ADC).

Figure 1: ADC values within the tumor are calculated from the diffusion-weighted data to approximate the number of tumor cells (*N*). ▾



- The value of the ADC largely depends on the number and separation of barriers that a diffusing water molecule encounters—providing an estimate of cellularity[2,4].
- MRI scans are collected at 4 times during the course of neoadjuvant therapy (NAT), consisting of two therapy regimens

Figure 2: All patients were treated with standard-of-care, where each patient received one therapy regimen followed by a second regimen and then surgery. Scans were collected to measure the affect of the drug after 1 cycle of therapy for each regimen. ▸

Individual patients were treated with courses of either paclitaxel followed by combination doxorubicin and cyclophosphamide or with that order reversed.

Mathematical Modeling

A reaction-diffusion model with logistic growth and mechanical coupling to tissue properties is defined as:

$$\frac{\partial N(\bar{x},t)}{\partial t} = \nabla\cdot\left(D\nabla\frac{N(\bar{x},t)}{\theta(\bar{x})}\right) + k\left(1-\frac{N(\bar{x},t)}{\theta(\bar{x})}\right)N(\bar{x},t) - \alpha C_{tissue}^{Drug}(\bar{x},t)N(\bar{x},t) \quad [1]$$

$$\text{and } D = D_0 e^{-\gamma\sigma_{vm}(\bar{x},t)}, \text{ where } \nabla\cdot G\nabla\vec{u} + \nabla\frac{G}{1-2\nu}(\nabla\cdot\vec{u}) - \lambda\nabla N(\bar{x},t) = 0, \text{ with}$$

variable *N* representing the tumor cell number; *D* is the diffusion (or movement) of the tumor cells with coefficient D_0 (global) mechanically coupled to the breast tissues using a linear elastic, isotropic equilibrium; *k* is the proliferation rate (global), θ the carrying capacity calibrated locally per voxel, and α the drug efficacy for each patient (global). The model is simulated using the finite difference scheme in 3D, and the Levenberg-Marquardt method is used for calibration of parameters.

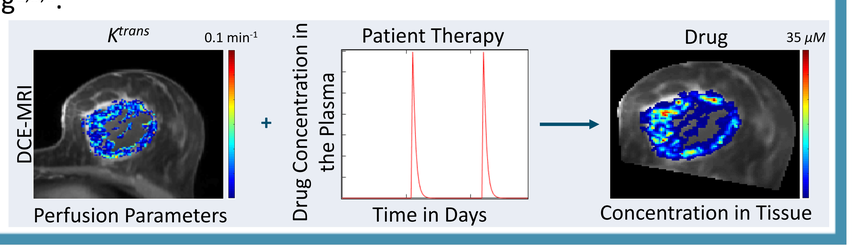
Drug delivery: DCE-MRI is used to estimate spatiotemporal changes in tumor vascularity for drug perfusion/delivery.

Using the physiological parameters (K^{trans}, v_e, v_p) describing the introduction, diffusion, and clearance of contrast agent throughout the tissue derived from the extended Kety/Tofts model and DCE-MRI data[1-3],

$$C_{tissue}(\bar{x},t) = K^{trans}(\bar{x})\int_0^t\left(C_{plasma}(u)e^{-\frac{K^{trans}(\bar{x})}{v_e(\bar{x})}(t-u)}\right)du + v_p(\bar{x})C_{plasma}(t), \quad [2]$$

we approximate the concentration of drug in the tissue using population derived concentration curves in the blood for each drug[1,5,6].

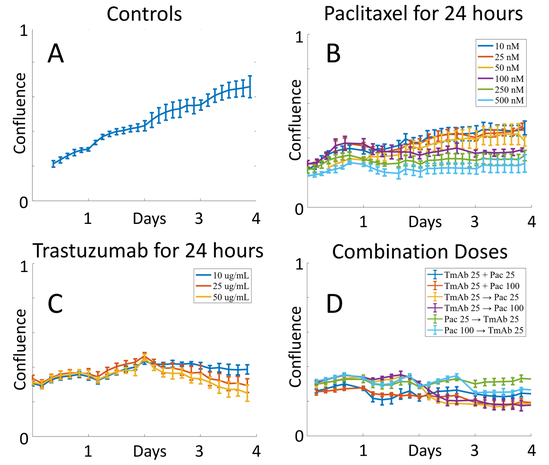
Figure 3: With each patient's DCE-MRI derived parameter maps representing the physiological features of the tumor vasculature and their individual therapy schedule, an approximate distribution of drug in the tumor is defined for each timepoint throughout NAT. ▸



Example of Preclinical Imaging Data and Cell Scale Model

Preclinical Data

- BT474 human derived breast cancer *in vitro* cell data (confluence) measured by time-resolved microscopy over the course of four days (Figure 4).
- Cultures are treated with a single dose of trastuzumab or paclitaxel on day 1 (after cells are plated for 24 hours).
- For combination doses, after the leading 24 hour dose on day 1, the other drug is given on day 2 for 24 hours. On day 3, the media is changed and all free drugs removed.



▲ Figure 4: Preliminary *in vitro* results for BT474 cell culture data. All error bars represent 95% confidence at each time point. Panel A depicts representative control results. Panel B shows data for paclitaxel dosages given for 24 hours (day 1 to day 2). Panel C shows three trastuzumab dosages given for 24 hours, and Panel D shows six different combinations of trastuzumab and paclitaxel doses given on days 1 and 2.

Mathematical Modeling

We define a set of three, ordinary differential equations for the *in vitro* data to describe the effects of timing and drug concentrations (equations [4] and [5]) on tumor cell (*N*) proliferation (equation [3]),

$$\frac{dN}{dt} = k(A_b,t)\left(1-\frac{N}{h(P_i,t)}\right)N \quad [3]$$

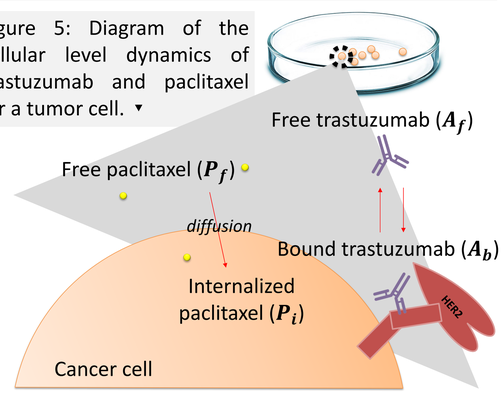
$$\frac{dA_b}{dt} = \beta_A(A_f - A_b)(N\cdot HER2_{exp} - A_b) \quad [4]$$

$$\frac{dP_i}{dt} = \alpha_P(P_f - P_i)N \quad [5]$$

$$k(A_b) = k_0\left(1-\eta_A A_b(t > t_A^*)\right) \quad [6]$$

$$h(P_i) = \theta - \left(\delta_P\left(e^{-g(t-t_P^*)} + S\right)P_i\right) \quad [7]$$

Figure 5: Diagram of the cellular level dynamics of trastuzumab and paclitaxel for a tumor cell. ▾



- Equations [4] and [5] simulate the binding (A_b) and the uptake (P_i) of free trastuzumab (A_f) and free paclitaxel (P_f), respectively (Figure 5).
- We define coupling terms for the growth (k) and carrying capacity (h) of the tumor cells (equations [6] and [7]) governed by trastuzumab and paclitaxel drug doses, respectively.
- Trastuzumab-HER2 binding decreases proliferation and after a period of time causes signaling cascades that can lead to further decrease in proliferation and cell death (equation [6]).
- Paclitaxel arrests or alters proliferation during mitosis (abnormal divisions) leading to changes in the overall cell population capacity (equation [7]).

Combining tissue and cellular scales

With the lessons learned from the *in vitro* scale, returning to the reaction-diffusion model, there are several potential mathematical couplings for cell death due to different drugs,

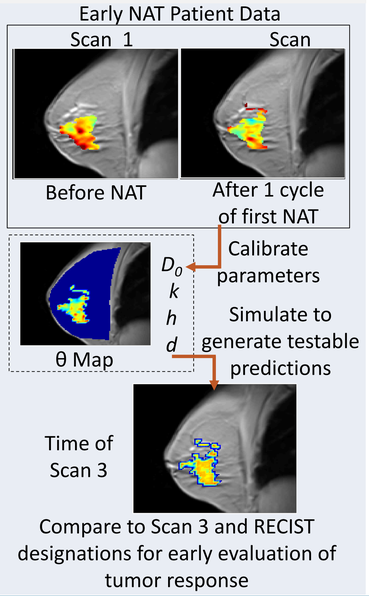
$$\frac{\partial N(\bar{x},t)}{dt} = \nabla\cdot\left(D\nabla\frac{N(\bar{x},t)}{\theta(\bar{x})}\right) + k(\bar{x},t)\left(1-\frac{N(\bar{x},t)}{h(\bar{x},t)}\right)N(\bar{x},t) - d(\bar{x},t)N(\bar{x},t)$$

where $k, h,$ and d are functions that depend on $C_{tissue}^{drug}(\bar{x},t)$ and their expressions defined according to tumor cell response dynamics per individual drug effect.

Next Steps:

- Collect additional *in vitro* cell response data and modeling results for standard-of-care breast cancer drugs.
- For each drug, create an extended model (or family of models)—where each new model extension is unique to each drug.
- Test models against the clinical data (Figure 6) and compare results across subgroups defined by similar first NAT regimens.

Figure 6: Calibrating and simulating the the extended mathematical model ▾



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